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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	PAPER NUMBER
1643	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/615,718	WALDMANN ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 02 June 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3 + 1* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1, 6-10, 12-15 and 17*.
   Claim(s) withdrawn from consideration: *15*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/David J Blanchard/
Primary Examiner, Art Unit 1643

Continuation of 11. does NOT place the application in condition for allowance because:
The objection to the disclosure as containing sequences that are encompassed by the sequences rules (37 C.F.R. §§ 1.821-1.825) and require sequence identifiers is maintained.
The response filed 6/2/2008 still does not address this requirement to comply with the sequence rules and as such the objection is maintained for reasons already of record (e.g., see item nos. 6-8 of the Office Action mailed 8/4/2006).

The rejection of claims 1, 6-10, 12-15 and 17 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The response filed 6/2/2008 again states that antibodies and peptides are known to those skilled in the art, and one skilled in the art can modify the antibody with a peptide by techniques that are known to those skilled in the art. According to applicant, once one skilled in the art modified the antibody with a peptide, one skilled in the art also would be able to determine, by techniques known to those skilled in the art, whether binding of the modified antibody to the therapeutic target had been reduced vis-à-vis the unmodified antibody. Applicant has shown, as acknowledged by the examiner, that one may modify the CAMPATH-1H antibody with the CD52 mimotope QTSSPSAD or QTSAAAVD and one skilled in the art would understand that other antibodies may be modified with peptides in a similar manner. Applicants' arguments have been fully considered but are not found persuasive for the reasons already of record and reiterated herein for brevity. Additionally, applciants' arguments appear to go more towards enableemnt, i.e., make and use, rather than adequate written description. The issue is not whether one skilled in the art could make and use anti-anti-idiotype antibodies, the issue is whether the '676 patent describes or discloses anti-anti-idiotype antibodies to an anti-idiotype antibody to a MN-specific antibody. Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. In re Barker, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (While acknowledging that some of its cases concerning the written description requirement and the enablement requirement are confusing, the Federal Circuit reaffirmed that under 35 U.S.C. 112, first paragraph, the written description requirement is separate and distinct from the enablement requirement and gave an example thereof.). An invention may be described without the disclosure being enabling (e.g., a chemical compound for which there is no disclosed or apparent method of making), and a disclosure could be enabling without describing the invention (e.g., a specification describing a method of making and using a paint composition made of functionally defined ingredients within broad ranges would be enabling for formulations falling within the description but would not describe any specific formulation). See MPEP 2161.
"It is not a question whether one skilled in the art might be able to construct the patentee's device from the teachings of the disclosure of the application. Rather, it is a question whether the application necessarily discloses that particular device." Id. at 536. University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (Fed. Cir. 2004).
Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991), with respect to the first paragraph of §112 the severability of its "written description" provision from its enablement ("make and use") provision was recognized by this court's predecessor, the Court of Customs and Patent Appeals, as early as In re Ruschig, 379 F.2d 990, 154 USPQ 118 (CCPA 1967). Although the appellants in that case had presumed that the rejection appealed from was based on the enablement requirement of §112, id. at 995, 154 USPQ at 123, the court disagreed: the question is not whether [one skilled in the art] would be so enabled but whether the specification discloses the compound to him, specifically, as something appellants actually invented. ... If [the rejection is] based on section 112, it is on the requirement thereof that "The specification shall contain a written description of the invention * * *." (Emphasis ours.) Id. at 995-96, 154 USPQ at 123 (first emphasis added). The issue, as the court saw it, was one of fact: "Does the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed]?" Id. at 996, 154 USPQ at 123. In a 1971 case again involving chemical subject matter, the court expressly stated that "it is possible for a specification to enable the practice of an invention as broadly as it is claimed, and still not describe that invention." In re DiLeone, 436 F.2d 1404, 1405, 168 USPQ 592, 593 (CCPA 1971) (emphasis added). As an example, the court posited the situation "where the specification discusses only compound A and contains no broadening language of any kind. This might very well enable one skilled in the art to make and use compounds B and C; yet the class consisting of A, B and C has not been described." Id. at 1405 n.1, 168 USPQ 593 n.1 (emphases in original). See also In re Ahlbrecht, 435 F.2d 908, 911, 168 USPQ 293, 296 (CCPA 1971) (although disclosure of parent application may have enabled production of claimed esters having 2-12 methylene groups, it only described esters having 3-12 methylene groups).
Clearly, one of skill in the art would not recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the single disclosed CAMPATH-1H-mimotope species. Therefore, only the humanized anti-CD52 antibody, CAMPATH-1H, linked to the CD52 mimotope QTSSPSAD or QTSAAAVD, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph and the rejection is maintained.

The rejection of claims 1, 6-10, 12-15 and 17 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising CAMPATH-1H (humanized anti-CD52 antibody), modified by linkage to a CD52 mimotope selected from QTSSPSAD and QTSAAAVD, does not reasonably provide enablement for all other therapeutic proteins and therapeutic antibodies modified (i.e., bound or linked) with just any other peptide or molecule (i.e., compound), wherein the therapeutic protein or therapeutic antibody has reduced side effects and produces a therapeutic effect by binding to the therapeutic target is maintained.

The response filed 6/2/2008 again submits that applicants' have modified the CAMPATH-1H antibody with two different mimotope peptides and once applicants' had proven the principle with the CAMPATH-1H antibody, one skilled in the art would know readily how to modify other antibodies with other peptides to reduce the binding of such antibodies to a therapeutic target. Applicant states that because applicants' have proven the principle with respect to the CAMPATH-1H antibody bound to two different mimotopes, one skilled in the art would

reasonably expect that other antibodies can be modified with other peptides to reduce binding of such antibodies to their respective therapeutic targets. Applicants' arguments have been fully considered but are not found persuasive for reasons already of record and reiterated herein for brevity. Again, while applicant has proven the principle that the CAMPATH-1H antibody modified with the CD52 mimotope QTSSPSAD or QTSAAAVD, reduces binding of CAMPATH-1H to CD52, reduces an immune response against the antibody and produces a therapeutic effect by binding to the therapeutic target CD52, applicant has not proven that the same principle is extendable to the broad scope of the claimed genus of therapeutic antibodies and peptide pairs, wherein the just any peptide reduces binding of a therapeutic antibody to a therapeutic target, reduces an immune response against the therapeutic antibody and produces a therapeutic effect by binding to the therapeutic target. Applicants' argument that the skilled artisan could modify other antibodies with other peptides to reduce the binding of such antibodies to a therapeutic target is not persuasive because the issue is make and use, not make and test to see if the skilled artisan could use. The specification does not enable the genus because where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one particular species, what other species will work. See MPEP 2164.03. The "principle" upon which applicant relies is limited to a humanized anti-CD52 antibody (CAMPATH-1H) linked to a CD52 mimotope (i.e., QTSSPSAD or QTSAAAVD), which reduces binding to CD52, but is competitively displaced by CD52 in vivo due to more favorable association and dissociation binding kinetics and the CAMPATH-1H-mimotope conjugate reduces cytokine release. However, the art points out that even minor changes in an epitope sequence may dramatically effect the antigen-binding function of an antibody. Lederman et al (Molecular Immunology 28:1171-1181, 1991, cited on PTO-892 mailed 8/4/06) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Li et al (Proc. Natl. Acad. Sci. USA 77:3211-3214, 1980, cited on PTO-892 mailed 8/4/06) disclose the dissociation of immunoreactivity from other activities when constructing analogs (see entire document). Therefore, even one amino acid difference in the peptide used for the modification of the therapeutic antibody could dramatically change the affinity or binding to the antibody combining site. The point is not that just because an antibody may not be able to bind to a modified epitope, the antibody is not enabled, the point is that the art provides evidence that one cannot predict the effect of minor changes within an epitope on antibody binding. Applicant has not provided any evidence or rationale which support the position that the particular properties and characteristics of the CAMPATH-1H-CD52 mimotope can be predictably extrapolated to the genus of peptides for modifying the genus of therapeutic antibodies and having the claimed properties and charcateristics. Applicant has not provided any guidance or direction as to how the properties of the CAMPATH-1H-CD52 mimotope interaction are predictive of the interaction between a particular therapeutic antibody and a given peptide sequence, such that the peptide modifies the therapeutic antibody to reduce binding to the therapeutic target, reduces an immune response against the therapeutic antibody and produces a therapeutic effect by binding to the therapeutic target. There is insufficient evidence or nexus between the properties of the CAMPATH-1H-CD52 mimotope interaction and making and using any other therapeutic antibody bound to just any peptide that inhibits binding of the therapeutic antibody to the therapeutic target, reduces an immune response against the therapeutic antibody, and wherein the antibody produces a therapeutic effect by binding to the therapeutic target.

In view of the broad scope of the claims at issue, the lack of the predictability of the art to which the invention pertains as evidenced by Lederman et al and Li et al, the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed pharmaceutical comprising a therapeutic antibody bound or linked to a peptide that inhibits binding of the therapeutic antibody to the therapeutic target, reduces an immune response against the therapeutic antibody, and produces a therapeutic effect by binding to the therapeutic target with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed pharmaceutical and absent working examples providing evidence which is reasonably predictive that the claimed pharmaceutical comprising a therapeutic antibody bound or linked to a peptide inhibits binding of the therapeutic antibody to the therapeutic target, reduces an immune response against the therapeutic antibody, and produces a therapeutic effect by binding to the therapeutic target, commensurate in scope with the claimed invention.

For these reasons and those already of record the rejection is maintained.

The rejection of claims 1, 6, 9-10 and 17 under 35 U.S.C. 102(b) as being anticipated by Hale G (Immunotechnology, 1:175-187, 1995, cited on PTO-892 mailed 8/4/2006) is maintained.

The response filed 6/2/2008 again states that the present invention is directed to a pharmaceutical comprising a therapeutic antibody that binds to a therapeutic target, wherein the therapeutic antibody is modified with a peptide that inhibits binding of the antibody to the therapeutic target and is effective for reducing an immune response against the antibody and for producing a therapeutic effect by binding to the therapeutic target. Applicant states that Hale teach a modified antibody as claimed by applicants. Applicants' arguments have been fully considered but are not found persuasive. The claims do not distinguish the modified antibody over the antibody of Hale. The claims merely require the antibody be modified with a peptide that reduces binding of the antibody to the therapeutic target, wherein the antibody includes an antibody combining site that binds to the therapeutic target and said peptide is bound to the antibody combinign site of said antibody. Thus, the CAMPATH-1H humanized antibody bound to the synthetic peptide, QTSSPSAD, is effective for reducing an immune response against the antibody and for producing a therapeutic effect by binding to the therapeutic target, does not distinguish the claimed pharmaceutical comprising a therapeutic antibody bound to a peptide that inhibits binding of the antibody to a therapeutic target, from the anti-CD52 humanized antibody, CAMPATH-1H, reversibly bound by the synthetic peptide, QTSSPSAD, a CD52 mimotope that inhibits binding of CAMPATH-1H to human lymphocytes expressing CD52 (i.e., "therapeutic target") by about four fold and the antibody is disclosed in various buffers including buffered saline (PBS) (i.e., reasonably interpreted to be a "pharmaceutically acceptable carrier") as taught by Hale. Amendign the claism to distinguish the modification from the prior art would overcome the insatnt rejection. Applciants' attention is directed to the fact that claim 9 is not anticipated by Hale.

For these reasons and those already of record, the rejection is maintained.

Then provisional rejection of claims 1, 6-10, 12-15 and 17 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 36-41 of copending Application No. 09/979,948 is maintained.

The response filed 6/2/2008 does not address this rejection and as such the rejection is maintained for reasons already of record.

The rejection of claims 1, 6-10, 12-15 and 17 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as introducing new matter is maintained.
The response filed 6/2/2008 does not address this rejection and as such the rejection is maintained for reasons already of record (e.g., see item no. 20 of the previous Office Action mailed 4/19/2007).

Respectfully,
/David J. Blanchard/
Primary Examiner, AU 1643
571-272-0827